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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,888	09/27/2005	David James Paterson	P-7945-US	8757

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,888	PATERSON, DAVID JAMES	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 9/28/2006 in response to office action mailed on 03/28/2006 has been acknowledged.

Claim 19 has been cancelled.

Claims 1, 2 and 18 have been amended.

Claims 1-18 *are pending and are examined in this office action. Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

(I). Rejection of claims **1-18** under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement has been withdrawn in view of applicants amendments to claims in response of 9/28/2006.

Claim Objection:

Claim 1 recites in line 4, "...which, when expressed, increases nitric acid synthase levels." makes the claim indefinite since the expression of the gene is a necessary event for the method to work. Changing said phrase to read for example as "wherein said gene is expressed to increase the NOS levels" is more suitable in the context.

Claim Rejections - 35 USC § 112 (second paragraph)

(II). Claim 1, and 3-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "cardiac autonomic structures" in claim 1 is used by the claim to mean "for e.g., vagus nerve, heart tissue (atrium) etc.,", while the accepted meaning is "all the sympathetic sytem (neural tissue) and myocardium involved in autonomic function of heart ." The term is indefinite because the specification does not clearly redefine the term.

Claim Rejections - 35 USC § 112 (First paragraph)

(III). Claims **1-18** stand rejected under 35 U.S.C. 112, first paragraph for the lack of enablement of the specification for the full scope of the claims for the reasons of record as set forth in the previous office action mailed 3/28/2006.

The above claims are directed to a method of treating a patient in need of increased vagal toning by delivering a nucleic acid molecule that increases the expression of nitric oxide synthase (NOS) into cardiac autonomic structures and to a pharmaceutical composition comprising nucleic acid molecules, when expressed in cardiac autonomic structures increases the level of NOS.

Response to Arguments (9/28/2006).

Applicant argues that an amendment made to claims 1 and 18 would over come above rejection. However, this is not found persuasive because the breadth of the claim still encompasses all routes and modes of delivery of the NOS encoding nucleic acid in the treatment of vagal tone increase. Further, scope of the claim encompasses all NOS synthetase coding sequences without providing information on how said sequences are expressed and thus implicitly encompassing all vectors (viral and non viral), promoters and enhancers and/or targeting functions etc. The specification however, only teaches an adenovirus vector based NOS-1 gene and delivery only by a direct injection into guinea pig or a rat atrial wall. Regarding NOS gene therapy of hear conditions Art only teaches the use of the direct injection method of delivering expressible NOS genes in to heart or

a neural tissue involved in cardiac sympathetic regulations in treating conditions such as bradycardia and hypertension and other related cardiac disorders. Given the unpredictability in the relevant art regarding the effectiveness of NOS gene therapy by administering the therapeutic gene by any route of adminsitration, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the claim encompassing any and/or all routes of NOS gene delivery for treating said vagal tone increase. Regarding claim to a pharmaceutical composition of NOS coding sequence, one of ordinary skill in the art would not know how to use it for treating any disease or disorder. At the best the specification is enabled for a method of treating for vagal toning by direct injection and expression in vagus nerve of an adenoviral vector encoding NOS-1 gene.

Claim Rejections - 35 USC § 102

Rejection of claims 1-3, 5, 13-16 under 35 USC 102 (a) as being anticipated by Kishi et al., (2002, Hypertension 39:264-268) has been withdrawn in view of applicants arguments and further in view of following new art rejections.

Claims 1-3, 5-6, 13-16 are rejected under 35 USC 102 (b) as being anticipated by Sessa et al., (WO 00/62605).

The above claims are directed to a method of treating a patient in need of increased vagal toning by delivering a nucleic acid molecule that increases the expression of nitric oxide synthase (NOS) into cardiac autonomic structures and to a pharmaceutical composition comprising nucleic acid molecules, when expressed in cardiac autonomic structures increases the level of NOS.

Regarding claims 1-2 and 5-6 Sessa teaches a composition of method of treating to prevent heart diseases including myocardial infraction, heart failure by NOS gene over-expression in cardiac structures including cardiac myocytes and arteries (p. 16-17, abstract) using a composition of adenoviral vector encoding a operably inserted eNOS

(NOS-3) or nNOS genes and their variants and delivered in vivo or in vitro (p.17, lines 1-5). Regarding claims 13-16 Sessa further teaches the delivery into murine and non-murine subjects using of adenoviral vectors among others (p.17, lines 7-30 bridging p.18). The cited art thus clearly anticipates the rejected claims.

Claims 1-3, 5, 13-16 are rejected under 35 USC 102 (b) as being anticipated by Sakai et al., (2000, Hypertension 36:1023-1028).

The above claims are directed to a method of treating a patient in need of increased vagal toning by delivering a nucleic acid molecule that increases the expression of nitric oxide synthase (NOS) into cardiac autonomic structures and to a pharmaceutical composition comprising nucleic acid molecules, when expressed in cardiac autonomic structures increases the level of NOS.

Regarding claims 1-2 and 5 Sakai teaches a composition of method of treating a rats by NOS gene over expression in nuclear tractus solitarii (NTS), containing endings of vagal neurons involved in autonomic cardiovascular regulation (p.1023, abstract) using a composition of adenoviral vector encoding a operably inserted bovine eNOS (NOS-3) gene and delivered in vivo by direct injection in to 6 sites in NTS (p.1024, col.1, 1st paragraph). Sakai further teaches that said gene therapy decreases blood pressure, decreases heart rate and decreases sympathetic nerve activity. Regarding claims 13-16 Sakai further teaches Adenoviral vector comprises DNA linked to an operable CMV promoter and SV40 poly adenylation site (p.1024, 2nd paragraph). The cited art thus clearly anticipates the rejected claims.

Claim Rejections - 35 USC § 103

Claims 6, 7, 9-11 13-19 are rejected under 35 USC 103 (a) as being unpatentable over Kishi et al., (2002, Hypertension 39:264-268), as applied to claims 1-3, 5, 13-16 as above in view of YI-FAN et al (2002, Am. J. Heart. Circ. Physiol. 282:H594-H601), Lonnerberg et al (1995, Proc.Natl. Acad Sci. USA 92: 4046-4050), Edelberg et al (2001, Heart 86:559-562) is withdrawn in view of the new rejections below.

Claims 6, 7, 9-11 13-18 are rejected under 35 USC 103 (a) as being unpatentable over Sakai et al., (2000, Hypertension 36:1023-1028) and Sessa et al., (WO 00/62605) as applied to claims 1-3, 5-6, 13-16 as above and further in view of Lonnerberg et al (1995, Proc.Natl. Acad Sci. USA 92: 4046-4050); Edelberg et al (2001, Heart 86:559-562).

The above claims are directed to a method of treating a patient in need of increased vagal toning by delivering a nucleic acid molecule that increases the expression of nitric oxide synthase (NOS) into cardiac autonomic structures and to a pharmaceutical composition comprising nucleic acid molecules, when expressed in cardiac autonomic structures increases the level of NOS.

Sakai and Sessa described above, however, do not teach the use of a cholinergic ganglia tissue specific promoter for NOS-1 gene expression, or non-viral gene therapy vector for targeted delivery in to heart.

Lonnerberg teaches regarding limitations of claims 9 and 18 of cholinergic specific promoter and methods of construction and use in the expression of reporter gene and tissue-specific expression in transgenic mice (p.4046, Abstract and p.4048, col.1, Table 1).

Edelberg teaches regarding limitations of claims 7, 10-11 and 13-16 a gene delivery by recombinant vectors containing naked DNA and gene expression by myocardial injection into right atrium of a pig heart to modulate heart rate (p.559, abstract and p.560, col.1, 3rd paragraph).

Thus it would have been obvious for one of ordinary skill in the art to substitute the promoter used for NOS in the gene therapy constructs of Sakai or Sessa with a cardiac targeting function, a cholinergic ganglia tissue specific promoter of Lonnerberg to specifically express the NOS transgene in cardiac ganglia and enhance the vagal toning. Further it would have been obvious for one of skill in the art to use a plasmid vector of Edelberg in place of adenoviral vector for delivery and expression of NOS gene direct injection in to the heart. One of skilled in the art would be motivated to use

a gene therapy vector constructs with NOS gene expression driven by a cholinergic tissue specific promoter because it prevents a heart disease by increasing the vagal toning, bradycardia etc by improving the tissue specific expression of the said therapeutic gene and further the use of a non-viral vector (or naked DNA) for gene delivery for the same increases the safety of the therapy by excluding viral vector related drawbacks. One of skilled in the art would have a reasonable of expectation success of using the NOS gene therapy vector with the above combination of features because the use of a tissue specific promoter or the use of a non-viral vector in vivo for gene therapy is routine in the art as taught above. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanna

Patent Examiner

Art Unit 1633

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER